REMARKS/ARGUMENTS

Claims 58-65 and 68-70 are pending in this application.

Applicants note and appreciate the withdrawal of the earlier objections and rejections under 35 U.S.C. §112, second paragraph, and 35 U.S.C. §102(e).

The remaining rejections of Claims 58-65 and 68-70 under 35 U.S.C. §§101 and 112, first paragraph, are addressed below.

I. Priority Determination

Applicants thank the Examiner for granting the priority of the instant application as February 18, 2000.

II. Claim Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

Claims 58-70 remain rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by a specific, substantial and credible asserted utility or a well-established utility." (See page 3 of the instant Office Action).

In particular, regarding the adipocyte glucose/FFA uptake assay (Example 117), the Examiner alleges that "PRO195 was found to inhibit glucose/free fatty acid uptake. No evidence is offered as to how an inhibitor in such an assay should be used." The Examiner further asserts that "it would be contrary that such inhibitory compounds would be therapeutically beneficial in treating any specific disease. Notably, inhibition of glucose/free fatty acid uptake is contrary to and works in the opposite direction to therapeutics related to insulin resistance and/or diabetes." The Examiner concludes that "the references and evidence via the cited references fails to note specific and substantial utility that is either asserted or well established and recognized in the art based upon uptake .5 that of insulin" (Page 6 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection. Applicants further submit, for the reasons set forth below, that the specification discloses at least one credible, substantial and specific asserted utility for the PRO195 polypeptide.

Applicants respectfully submit that claims 66-67 were canceled by amendment in the Response to Office Action filed December 30, 2004. Accordingly, the rejection of these claims is moot.

Utility – Legal Standard

According to 35 U.S.C. § 101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. (Emphasis added.)

In interpreting the utility requirement, in *Brenner v. Manson*[1] the Supreme Court held that the quid pro quo contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent applicant disclose a "substantial utility" for his or her invention, i.e. a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

---

[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

In *Cross v. Iizuka*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, i.e. there is a reasonable correlation there between."[7] The court perceived "No insurmountable difficulty" in finding that, under appropriate circumstances, "in vitro testing, may establish a practical utility."[8]

The case law has also clearly established that applicants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face. [9] The PTO has the initial burden that applicants' claims of usefulness are not believable on their face.[10] In general, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11], [12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the

---

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984).

totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines")[15], which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "'substantial'" utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill

---

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II (B)(1).

in the art, do not impose a rejection based on lack of utility."

Utility – Application of Standard

The specification provides sufficient disclosure to establish a specific, substantial and credible utility for the PRO195 polypeptide for the reasons previously set forth in the Applicants' response filed on December 30, 2004, and below.

The Examiner asserts that "PRO195 was found to inhibit glucose/free fatty acid uptake. No evidence is offered as to how an inhibitor in such an assay should be used." The Examiner further asserts that "it would be contrary that such inhibitory compounds would be therapeutically beneficial in treating any specific disease. Notably, inhibition of glucose/free fatty acid uptake is contrary to and works in the opposite direction to therapeutics related to insulin resistance and/or diabetes." The Examiner concludes that "the references and evidence via the cited references fails to note specific and substantial utility that is either asserted or well established and recognized in the art based upon uptake .5 that of insulin" (Page 6 of the instant Office Action).

The Examiner states that the references previously cited by Applicants show that agents which increase glucose transport are useful in the treatment of disorders such as diabetes. Applicants respectfully point out that the fact that PRO195 inhibits glucose uptake does not make it useless in such treatment. One of skill in the art would readily understand that a protein which inhibits glucose uptake into adipocytes is a potential therapeutic target, since blocking the function of this protein would decrease the inhibition, and thus increase glucose uptake into adipocytes. Accordingly, the claimed PRO195 polypeptides are useful in the therapeutic treatment of disorders wherein stimulation of glucose uptake by adipocytes is expected to be therapeutically effective, such as obesity, diabetes, and hyper- or hypo-insulinemia.

Applicants also point out that Mueller *et al.* (1998) disclose that inhibitors of adipocyte glucose uptake, including 2-DG, phloretin, and cytocholasin B, inhibit leptin gene expression and leptin secretion from adipocytes. It was known in the art at the time of filing that leptin is involved in the regulation of food intake, energy expenditure, and body fat stores, and that leptin

decreases after fasting or caloric restriction and increases a number of hours after refeeding. (Mueller *et al.* (1998), p. 551, col. 1). One of skill in the art would therefore have understood that agents capable of modulating leptin regulation would be useful in investigations regarding the treatment of obesity. Similarly PRO195, as an inhibitor of adipocyte glucose uptake, would be useful as a pharmacological tool for investigation of leptin regulation, in the same way as agents already known and used in the art such as 2-DG, phloretin, and cytocholasin B.

As discussed above, the M.P.E.P. states that, "any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a '"substantial" utility' (M.P.E.P. §2107.01). The Guidelines for Examination of Applications for Compliance With the Utility Requirement instruct that: "[i]f the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility" (M.P.E.P. §2107 II (B)(1)).

Accordingly, Applicants respectfully submit that at the effective filing date of the instant application, one of skill in the art would have reasonably accepted that various compounds, such as PRO195, that are capable of modulating glucose uptake, have a substantial, practical, real life utility. The above-mentioned studies have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify therapeutic agents for treating diseases and conditions such as obesity, diabetes, hyper- or hypo-insulinemia, or pharmacological tools for the study of these diseases and conditions. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as study and treatment of glucose uptake related diseases, including obesity and diabetes, are envisioned for the claimed PRO195 polypeptide based on the glucose/FFA uptake assay results disclosed herein.

In view of the above, Applicants respectfully submit that the specification discloses at least one credible, substantial and specific asserted utility for the PRO195 polypeptide. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed PRO195 polypeptide.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present utility rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

III. Claim Rejections – 35 U.S.C. §112, First Paragraph (Written Description)

Claims 58-70 remain rejected under 35 U.S.C. §112, first paragraph, for allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention." In particular, the Examiner notes that "the claims as written include polypeptides having at least 80-99% sequence identity with SEQ ID NO:330 and polypeptides including or lacking various regions including, lacking its signal peptide, the extracellular domain, the extracellular domain but lacking its signal peptide, but for which no particular biological activity or function is recited." Therefore the Examiner asserts that "the instant disclosure of a single polypeptide, that of SEQ ID NO:330 with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera." (Page 7 of the instant Office Action).

Applicants respectfully disagree and traverse the rejection. For the reasons discussed below, Applicants respectfully submit that Claims 58-65 and 68-70 satisfy the written description requirement under 35 U.S.C. §112, first paragraph

Applicants submit that claims 66-67 were canceled by amendment in the Response to Office Action filed December 30, 2004. Accordingly, the rejection of these claims is moot.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the

specification for the claim language."[18] [19];. The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[20] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [21] [22]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[23] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[24] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[25] [26].

---

[18] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983).

[19] *See also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991).

[20] *See e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.

[21] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000).

[22] *See also* M.P.E..P. §2163 II(A).

[23] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).

[24] *See also* M.P.E.P. §2141.03.

[25] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added).

[26] *See also* M.P.E.P. §2141.03.

The specification provides sufficient written description for the claimed invention

First, Applicants respectfully maintain the position that that Claims 58-65 and 68-70 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on December 30, 2004.

Secondly, Applicant respectfully submit that Claim 63 (and, as a consequence, those claims dependent from the same), directed to the polypeptide of SEQ ID NO:330, with or without its signal peptide sequence, meets the written description requirement under 35 U.S.C. §112, first paragraph. The Examiner acknowledges that Applicants have described the polypeptide sequence of SEQ ID NO:330. (Page 7 of the instant Office Action). As disclosed, for example, in Figure 132, the signal peptide sequence of SEQ ID NO:330 comprises amino acid residues 1-31. Neither Claim 63 nor any other claim recites the extracellular domain of the polypeptide.

Applicants respectfully submit that the instant specification evidences the actual reduction to practice of a full-length PRO195 polypeptide of SEQ ID NO:330, with or without its signal peptide sequence. As stated above, the Examiner has acknowledged that a polypeptide comprising the sequence set forth in SEQ ID NO:330 meets the written description provision of 35 U.S.C. §112, first paragraph. Thus, the genus of polypeptides with at least 80% sequence identity to SEQ ID NO:330, which possess the functional property of inhibiting the uptake of glucose or FFA by adipocyte cells would meet the requirement of 35 U.S.C. §112, first paragraph, as providing adequate written description.

The specification describes methods for the determination of percent identity between two amino acid sequences. (See page 123, line 24 to page 125, line 14). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. The specification further provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 9 to page 183, line 8) This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). The specification describes methods for one of ordinary skill in the art to identify polypeptides having at least 80% identity to SEQ ID

NO:330 wherein the polypeptide inhibits the uptake of glucose or FFA by adipocyte cells. Specifically, Example 117 sets forth an assay for determining whether a native polypeptide having at least 80% identity to PRO195 inhibits the uptake of glucose or FFA by adipocyte cells. Thus one of ordinary skill in the art would have understood at the time of filing what was encompassed by the claims.

As noted by the Examiner, a description of a genus of cDNAs "may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus." As discussed above, Applicants have recited structural features, namely, 80% sequence identity to SEQ ID NO:330, which are common to the genus. The genus of claimed polypeptides is further defined by having a specific activity, inhibition of the glucose and/or FFA uptake by adipocyte cells. Accordingly, a description of the claimed genus has been achieved.

The Examiner asserts that "the specification provides only a single sequence which provides for such inhibition and fails to describe what other sequences inhibit," and that "there is no description or guidance as to how similar the other related sequence need to be such that the variability in structure correlates to inhibition or some other known and useful function." As discussed above, the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity, including a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Furthermore, the claims require that the polypeptide variants retain the functional activity of PRO195, and the specification provides an assay for this activity. Thus the specification has provided all the guidance needed to permit one of skill in the art to understand what is encompassed by the claimed genus of polypeptide variants, and that Applicants were in possession of the claimed genus of polypeptide variants at the time of filing.

Accordingly, the specification provides adequate written description for native polypeptides having at least 80% identity to SEQ ID NO:330 wherein the polypeptide inhibits the uptake of glucose or FFA by adipocyte cells. For the above reasons, Applicants respectfully

request the Examiner to reconsider and withdraw the written description rejections under 35 U.S.C. §112, first paragraph.

IV. Claim Rejections Under 35 U.S.C. §112, First Paragraph (Enablement)

Claims 58-70 remain rejected under 35 USC § 112, first paragraph, as failing to enable a person of skill in the art to make and use the invention commensurate in scope with the claims. In particular, the Examiner asserts that "the specification does not reasonably provide enablement for the variable peptide sequences and for such generic sequences where no requisite functional activity is provided as claimed." (See page 10 of the instant Office Action.)

Applicants respectfully disagree and traverse the rejection. For the reasons discussed below, Applicants respectfully submit that Claims 58-65 and 68-70 satisfy the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicants submit that claims 66-67 were canceled by amendment in the Response to Office Action filed December 30, 2004. Accordingly, the rejection of these claims is moot.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation. ([27] [28]. Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[29] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[30] [31]

---

[27] M.P.E.P. §2164.01.

[28] *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)).

[29] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (C.C.P.A. 1976).

[30] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (C.C.P.A. 1977).

[31] M.P.E.P. §2164.06.

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification, 4) the state of the prior art, and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[32] [33]. "Limitations and examples in the specification do not generally limit what is covered by the claims" M.P.E.P. § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[34]

The specification provides sufficient information to enable the claimed invention

First, Applicants respectfully maintain the position that that Claims 58-65 and 68-70 satisfy the written description requirement under 35 U.S.C. §112, first paragraph, for the reasons previously set forth in the Applicants' response filed on December 30, 2004.

Secondly, Applicant respectfully submit that Claim 63 claims the full-length polypeptide of SEQ ID NO:330, with or without its signal peptide sequence. As disclosed, for example, in

---

[32] M.P.E.P. §2164.08.

[33] *In re Marzocchi*, 439 F.2d 220, 223-4, 169 USPQ 367, 370 (C.C.P.A. 1971).

[34] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1372 (Fed. Cir. 1999) (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991)).

Figure 132, the signal peptide sequence of SEQ ID NO:330 comprises amino acid residues 1-31. Neither Claim 63 nor any other claim recites the extracellular domain of the polypeptide. Applicants have clearly provided the full-length sequence of SEQ ID NO:330 for the PRO195 polypeptide, thus one skilled in the art would easily know how to make the polypeptide, with or without the identified signal peptide sequence. In addition, as mentioned above, PRO195 was demonstrated to inhibit the uptake of glucose or FFA by adipocyte cells. Therefore, based on this information one skilled in the art would have known at the time of filing how to use the full-length PRO195 polypeptide (SEQ ID NO:330) in the therapeutic treatment of disorders wherein stimulation of glucose uptake by adipocytes is expected to be therapeutically effective, such as obesity, diabetes, and hyper- or hypo-insulinemia, or as a pharmacological tool for the study of these diseases and conditions.. Accordingly, Claim 63 (and, as a consequence, those claims dependent from the same) meets the enablement requirement under 35 U.S.C. §112, first paragraph.

Applicants have provided native PRO195 sequence SEQ ID NO:330. The present application also describes methods for identifying polypeptides which inhibit the uptake of glucose or FFA by adipocyte cells. Example 117 of the present application provides a detailed protocol for the adipocyte glucose/FFA uptake assay. By following the disclosure in the specification, one skilled in the art can easily test whether a variant PRO195 protein is an inhibitor of glucose uptake. The specification further describes methods for the determination of percent identity between two amino acid sequences. (See page 123, line 24 to page 125, line 14). In fact, the specification teaches specific parameters to be associated with the term "percent identity" as applied to the present invention. Accordingly, one of skill in the art could identify whether the variant PRO195 native sequence falls within the parameters of the claimed invention. Once such an amino acid sequence was identified, the specification sets forth methods for making the amino acid sequences (see page 180, line 9 to page 184, line 35) and methods of preparing the PRO polypeptides (see page 184, line 37 and onward).

Therefore, Applicants respectfully submit that one of skill in the art could readily test a variant polypeptide to determine whether it inhibits the uptake of glucose or FFA by adipocyte

cells by the methods set forth in Example 117. Furthermore, one of ordinary skill in the art has a sufficiently high level of technical competence to identify sequences with at least 80% identity to SEQ ID NO:330. Accordingly, one of ordinary skill could practice the claimed invention without undue experimentation.

The Examiner asserts that the specification "does not enable this broad scope of the claims that encompasses a multitude of analogs or equivalents because the specification does not teach which residues can or should be modified such that the polypeptides retain sufficient structural similarity to evoke activity." Applicants respectfully disagree. Applicants respectfully point out that the specification provides detailed guidance as to changes that may be made to a PRO polypeptide without adversely affecting its activity (page 180, line 9 to page 183, line 8) This guidance includes a listing of exemplary and preferred substitutions for each of the twenty naturally occurring amino acids (Table 6, page 182). Furthermore, the claims require that the polypeptide variants retain the functional activity of PRO195, and the specification provides an assay for this activity. Thus the specification has provided all the guidance needed to permit one of skill in the art to make and use the claimed variant native sequence polypeptides.

The Examiner further asserts that the specification "provides no guidance as to which of the essentially infinite possible choices is likely to be successful and the skilled artisan would not necessarily expect functional conservation among homologous sequences." Applicants have provided the sequence of native PRO195 sequence, SEQ ID NO:330. As indicated above, given the guidance provided in the specification, one skilled in the art could readily generate variants having at least 80% identity to the PRO195 sequence. It would be a simple matter for one skilled in the art to test the polypeptides to see if they inhibit the uptake of glucose or FFA by adipocyte cells using the methods of Example 117. This would not require undue experimentation.

The claims currently recite peptide sequences associated with a biological activity. This biological activity together with the well defined relatively high degree of sequence identity and general knowledge in the art at the time the invention was made, sufficiently defines the claimed genus such that, one skilled in the art, at the effective date of the present application, would have known how to make and use the claimed polypeptide sequences without undue experimentation.

As the M.P.E.P. states, "[t]he fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation."[35]

As discussed above, a considerable amount of experimentation is permissible, if it is merely routine. Applicants submit that the identification of variant native PRO1780 polypeptides having at least 80% identity to SEQ ID NO:330 wherein the polypeptide inhibits the uptake of glucose or FFA by adipocyte cells can be performed by techniques that were well known in the art at the priority date of this application, and that the performance of such work does not require undue experimentation.

The Examiner asserts that allegedly "no utility is noted for the related molecules based upon testing positive for inhibiting glucose and/or free fatty acid uptake." As discussed above (see the section discussing the rejections under 35 U.S.C. §101), studies described in literature previously made of record have clearly established that the glucose/FFA uptake assay as described in the instant application is a reliable assay system to identify therapeutic agents for treating diseases and conditions such as obesity, diabetes, hyper- or hypo-insulinemia, or pharmacological tools for the study of these diseases and conditions. Therefore, Applicants respectfully submit that a variety of real-life utilities, such as study and treatment of glucose uptake related diseases, including obesity and diabetes, are envisioned for the claimed PRO195 polypeptide and polypeptide variants having 80% sequence identity to PRO195, based on testing positive as an inhibitor in the glucose/FFA uptake assay disclosed herein.

In view of the above, Applicants respectfully submit that based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to both make and use the claimed PRO195 polypeptide variants.

For the above-noted reasons, Applicants respectfully request the Examiner to reconsider and withdraw the enablement rejections under 35 U.S.C. §112, first paragraph.

---

[35] M.P.E.P. §2164.01 citing *In re Certain Limited-charge Cell Culture Microcarriers,* 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff' sub nom. Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985).

CONCLUSION

All claims pending in the present application are believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39780-2630 P1C3**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: June 9, 2005

By: _____
Barrie D. Greene (Reg. No. 46,740)

HELLER EHRMAN, LLP
275 Middlefield Road
Menlo Park, California 94025-3506
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 2125979 v1
6/9/05 9:50 AM (39780.2630)